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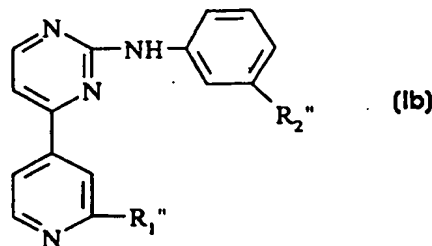
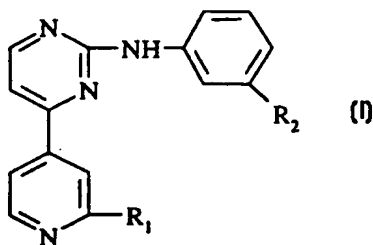
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(54) Title: PYRIDINYLPYRIMIDINE AMINES AS IMMUNOGLOBULINE E (IgE) SYNTHESIS INHIBITORS



(57) Abstract

Use of the compounds of formula (I) wherein R_1 is halogen, phenyl or alkyl and R_2 is hydrogen, halogen, alkyl, alkoxy or trifluoromethyl, in free form or salt form, in the treatment of IgE-mediated diseases, including i.a. chronic transplant rejection. The compounds of formula (I) are partly known. A subgroup thereof, namely the compounds of formula (Ib) wherein either R_1' is halogen of atomic number 17 or 35 and R_2'' is hydrogen or alkoxy, or R_1'' is phenyl or alkyl and R_2'' is hydrogen, halogen, alkyl, alkoxy or trifluoromethyl, is novel and possesses remarkable cell type specificity. The compounds of formula (Ib) may be prepared e.g. by chlorination or bromination in adjacent position to an N-oxido group or by reaction of the resultant chloro or bromo compound with an organometallic compound.

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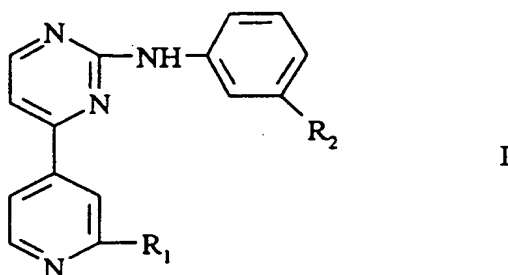
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PYRIDINYLPYRIMIDINE AMINES AS IMMUNOGLOBULINE E (IgE) SYNTHESIS INHIBITORS

The invention relates to pyridinylpyrimidine amines.

It concerns a novel pharmaceutical use of the compounds of formula I



wherein

R₁ is halogen, phenyl or alkyl and

R₂ is hydrogen, halogen, alkyl, alkoxy or trifluoromethyl,

in free form or salt form.

A compound of formula I may be present in free form as base or, where such forms exist, in salt form, particularly acid addition salt form. A compound of formula I in free form may be converted into a salt form in conventional manner and vice-versa.

Halogen preferably is of atomic number 17 or 35, especially chlorine. Phenyl preferably is unsubstituted or substituted by halogen, alkyl or alkoxy. When it is substituted, it preferably is mono- or disubstituted, preferably monosubstituted. Phenyl preferably is unsubstituted. Alkyl and alkoxy preferably independently are of 1 to 4 carbon atoms, they especially are of 1 or 2, even more preferably of 1 carbon atom.

R₁ and R₂ preferably are, independently, halogen, preferably chlorine, or alkyl, preferably methyl; more preferably, either R₁ and R₂ are both independently halogen, preferably chlorine, or R₁ and R₂ are both independently alkyl, preferably methyl.

In a subgroup of compounds of formula I R₁ is phenyl and R₂ is as defined above.

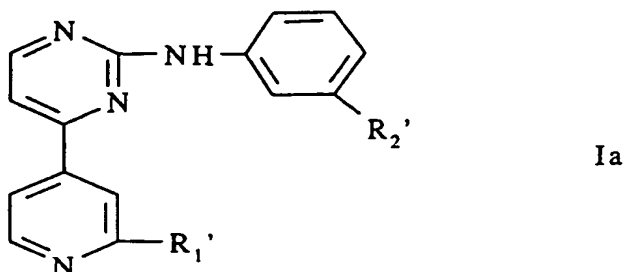
A preferred subgroup of compounds of formula I (**compounds Is**) is the compounds of formula I wherein

R₁ is chlorine, unsubstituted phenyl or alkyl of 1 or 2 carbon atoms, and

R₂ is hydrogen, chlorine, methyl, methoxy or trifluoromethyl,

in free form or salt form.

The compounds of formula I are partly known. The compounds of formula Ia



wherein

R₁' is halogen, and

R₂' is halogen, lower alkyl or trifluoromethyl,

their preparation and their use as protein kinase inhibitors in the treatment of, in particular, tumor diseases and further conditions wherein protein kinases are involved, are described in Ciba-Geigy WO 95/09851 and/or Ciba-Geigy WO 95/09853.

In a subgroup of compounds of formula Ia in free form or salt form (**compounds Iap**) R₁' is halogen and R₂' is halogen or lower alkyl.

Immunoglobulin E (IgE) is critically involved in the pathogenesis and maintenance of allergic diseases such as atopic dermatitis, allergic asthma, allergic conjunctivitis and allergic rhinitis. To date, patients suffering from atopic dermatitis are mainly treated with local or systemic glucocorticoids, ultraviolet light or, in severe cases, with immunosuppressants such as cyclosporin. Allergic asthma patients are mainly treated with glucocorticoids or theophylline. These compounds suffer from various side effects and are not achieving the goal of reversal of disease progression in addition to alleviation of symptoms. It has been demonstrated recently that interference with IgE production or inactivation of its effector function once it has been synthesized in the body, reduces allergic immune response and, consequently, leads to amelioration of the disease. However, no specific inhibitors of IgE production in human B-lymphocytes are commercially available yet.

It has now been found that, surprisingly, the compounds of formula I in free form or salt form act as specific inhibitors of IgE synthesis. Upon systemic or oral administration they strongly suppress immunoglobulin synthesis, in particular the synthesis of immunoglobulin E in B-lymphocytes, i.e. they exhibit isotype specificity. Further, inhibition occurs in a cell-type specific manner.

These activities can be shown in the following assays. The following abbreviations are used:

ELISA	= enzyme-linked immunosorbent assay
FACS	= fluorescence-activated cell sorting
HaCat	= cell line originating from human adult skin keratinocytes propagated under low calcium conditions and elevated temperature
IgE	= immunoglobulin E
IL-4	= interleukin-4
IMDM	= Iscove's modified Dulbecco medium
SRBC	= sheep red blood cells
TNF- α	= tumor necrosis factor - α
TPA	= O-tetradecanoylphorbol 13-acetate

1. Isotype specificity: Inhibition of immunoglobulin synthesis induced in primary human B-lymphocytes stimulated by IL-4 with added anti-CD40 antibody:

Normal human B-lymphocytes are purified from tonsils by removing contaminating T-cells with SRBC-rosetting according to M.S. Weiner et al., Blood 42 (1973) 939. The resulting B-cells are more than 95 % pure as judged by CD19 expression in a FACS analysis. Using 96-well round-bottomed microtiter plates (Costar) 5×10^4 B-cells are set up in a final volume of 200 μ l/well in IMDM. After pre-incubation with test compound for one hour the cells are cultured to induce IgE production for 9 days at 37°C in air supplied with 5 % CO₂ in the presence of 50 ng/ml of IL-4 and 500 ng/ml of anti-CD40 antibody. The culture cell supernatants are collected and quantitated for IgE, IgG1 and IgM by standard isotype specific sandwich ELISA.

In this test the compounds of formula I in free form or salt form inhibit IgE production preferentially over IgG (IgG1) and IgM with 50 % inhibitory concentrations (IC₅₀ values) of from about 0.5 nM to about 200 nM.

Similar results are obtained when total splenocytes are used as primary B-cell source.

2. Cell type specificity: Inhibition of proliferation of various cell types:

- a) HMEC-1 cells are incubated with increasing amounts of test compound overnight and subsequently stimulated with TNF- α for 16 hours to induce VCAM-1 expression. After fixation, VCAM-1 positivity is quantitated using an immunohistochemical method. To evaluate anti-proliferative effects of test substances cell numbers are counted by Giemsa dye staining.
- b) HaCat cells are incubated for 3 days with increasing concentrations of test substance. Cell proliferation is measured using a sulforhodamine B - based colorimetric assay.
- c) Cytokine production in the T-helper cell clones MoT81 and ChT38 is induced with anti-CD3 monoclonal antibody and TPA for 24 hours in the presence of test compound. IL-2, IL-3, IL-4, IL-5, IL-10 and IFN- γ are quantitated in the supernatants by ELISA.
- d) Monocyte-derived dendritic cells are co-cultivated with superantigen- or specific allergen- stimulated autologous or allogeneic T-cells for 4 days with increasing concentrations of test compound. The stimulation of T-cell proliferation by antigen-presenting dendritic cells is determined by pulsing with ^3H -thymidine for the last 16 hours.

In this test the compounds of formula I in free form or salt form inhibit constitutive proliferation of the above endothelial keratinocyte and T-lymphocyte cell lines with IC_{50} values of from about 400 nM to more than 5000 nM, well above the concentrations needed to block IgE synthesis.

The compounds of formula I in free form or pharmaceutically acceptable salt form are therefore indicated for use as inhibitors of immunoglobulin synthesis, especially inhibitors of IgE synthesis, in the treatment of **IgE-mediated diseases**, particularly IgE-mediated allergic diseases, such as **atopic dermatitis**, particularly in children, **urticaria**, particularly acute urticaria, **allergic asthma**, **allergic rhinitis**, **food allergies**, **allergic conjunctivitis**, **hayfever**, **bullous pemphigoid**, **industrial sensitization** and **chronic rejection of transplants**.

For the above uses the dosage to be used will vary, of course, depending e.g. on the particular compound employed, the mode of administration and the treatment desired. However, in general satisfactory results are obtained when the compounds are administered at a daily dosage of from about 1 mg/kg to about 30 mg/kg animal body weight, suitably given in divided doses two to four times daily. For most larger mammals the total daily dosage is from about 70 mg to about 2000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Unit dosage forms comprise, for example, from about

17.5 mg to about 1000 mg of compound in admixture with at least one solid or liquid pharmaceutically acceptable carrier or diluent.

A compound of formula I in free form or pharmaceutically acceptable salt form may be administered in similar manner to known standards such as glucocorticoids and antihistaminics for use in such indications. It may be admixed with conventional chemotherapeutically acceptable carriers and diluents and, optionally, further excipients, and administered e.g. orally in such forms as tablets and capsules.

Alternatively, it may be administered topically in such conventional forms as aerosols, ointments or creams, parenterally or intravenously. The concentration of active substance will, of course vary depending e.g. on the compound employed, the treatment desired and the nature of the form. In general, however, satisfactory results are obtained in topical application forms at concentrations of from about 0.05 % to about 5 %, particularly from about 0.1 % to about 1 % by weight.

The invention thus comprises the use of a compound of formula I in free form or salt form **in the preparation of a medicament** for the therapy of IgE-mediated diseases.

Pharmaceutical compositions for use in the therapy of IgE-mediated diseases may be prepared by mixing a compound of formula I in free form or pharmaceutically acceptable salt form together with at least one pharmaceutically acceptable carrier or diluent.

The invention further includes a **method of treatment** of IgE-mediated diseases which comprises administering a therapeutically effective amount of a compound of formula I in free form or pharmaceutically acceptable salt form to a subject in need of such treatment. A subject in need of such treatment may e.g. be a patient not suffering from, or not treated for, a tumor disease or further condition where protein kinases are involved, or not otherwise undergoing treatment for elevation of depressed immune responses associated with therapy.

The compounds of formula I in free form or pharmaceutically acceptable salt form are well tolerated, as may be determined in conventional manner.

The most preferred compounds of formula I in these indications are:

- a) N-(3-chlorophenyl)-N-[4-(2-chloropyridin-4-yl)pyrimidin-2-yl]amine (Compound A; of formula Ia; Example 1 in WO 95/9851); and
- b) N-(3-methylphenyl)-N-[4-(2-methylpyridin-4-yl)pyrimidin-2-yl]amine (Compound B; of formula Ib hereunder; see Example 2).

For Compound B the IC_{50} in the above assay 1. is from about 0.5 nM to about 10 nM. The following activity has for example be determined in the above assay 1.:

Compound	R_1	R_2	IC_{50} (nM)		
			IgE	IgG ₁	IgM
A	Cl	Cl	7.2 ¹⁾	150	300
B	CH ₃	CH ₃	2 ¹⁾	> 300	> 300

¹⁾ In an earlier experiment, an IC_{50} value of 0.5 nM was obtained

Further compounds of formula I are e.g.:

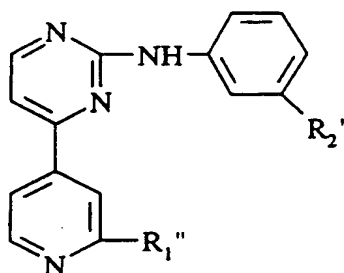
c) N-(3-methylphenyl)-N-[4-(2-chloropyridin-4-yl)pyrimidin-2-yl]amine

(Compound C; $R_1 = Cl$, $R_2 = CH_3$; Example 15.2 in WO 95/9853); and

d) N-(3-trifluoromethylphenyl)-N-[4-(2-chloropyridin-4-yl)pyrimidin-2-yl]amine

(Compound D; $R_1 = Cl$, $R_2 = CF_3$; Example 2 in WO 95/9851).

It has also been found that, although cell type specificity of the compounds of formula I is high, the level of specificity is particularly remarkable for a subgroup of compounds of formula I which is novel and also forms part of the present invention, namely the compounds of formula Ib



Ib

wherein

either R_1'' is halogen of atomic number 17 or 35 and

R_2'' is hydrogen or alkoxy,

or R_1'' is phenyl or alkyl and

R_2'' is hydrogen, halogen, alkyl, alkoxy or trifluoromethyl,

in free form or salt form.

The invention thus also concerns a **compound of formula Ib** in free form or salt form.

It further concerns a **compound of formula Ib** in free form or pharmaceutically acceptable salt form for use as a **pharmaceutical**, and a **pharmaceutical composition** comprising a compound of formula Ib in free form or pharmaceutically acceptable salt form together with at least one pharmaceutically acceptable carrier or diluent.

R_1'' preferably is halogen of atomic number 17 or 35 or alkyl, preferably chlorine or methyl, especially methyl. R_2'' preferably is halogen or alkyl, preferably halogen of atomic number 17 or 35, especially chlorine, or methyl; it especially is methyl. Even more preferably, R_1'' and R_2'' are both methyl.

A preferred subgroup of compounds of formula Ib (**compounds Ibs**) is the compounds of formula Ib wherein

either R_1'' is chlorine and

R_2'' is hydrogen or methoxy,

or R_1'' is phenyl, methyl or ethyl and

R_2'' is hydrogen, chlorine, methyl, methoxy or trifluoromethyl,

in free form or salt form.

In a further subgroup of compounds of formula Ib in free form or salt form (**compounds Ibp**) R_2'' is other than hydrogen.

The remarkable cell type specificity of the compounds of formula Ib is apparent e.g. from a collection of the IC_{50} values obtained with the preferred compound of formula Ia and with the preferred compound of formula Ib for inhibition of cell proliferation in various cell types and assays, and their comparison with the IC_{50} values obtained for inhibition of IgE synthesis in human B-lymphocytes, as appears from the following Table:

Comparison of
IC₅₀ values obtained for IgE synthesis inhibition with
IC₅₀ values found to impair cell proliferation (nM)

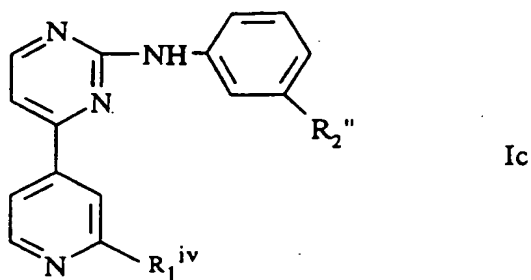
Assay	Compound A (IC ₅₀)	Compound B (IC ₅₀)
IgE synthesis	7.2	2
<u>Cell proliferation:</u>		
Primary B-cells (IL-4/anti-CD40 induced)	772	1090
Primary T-cells (dendritic cell induced)	405	1137
HaCat cells (constitutive)	3300	2500
BL2 cells (constitutive)	426	1073
HMEC-2 cells (constitutive)	6350	2450
U266 cells (constitutive)	3869	> 5000
IM9 cells (constitutive)	942	3300

The results show that, compared to inhibition of IgE synthesis, a more than 500fold concentration of Compound B is necessary to impair either induced or constitutive growth of all cell types tested, as compared to an about 60fold concentration for Compound A: thus the window of specificity is approximately 10 times larger for novel Compound B than for known Compound A.

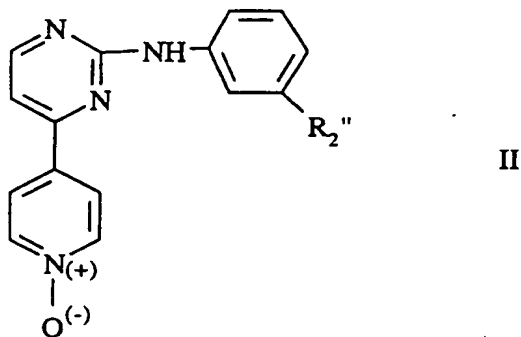
Further, the compounds of formula Ib possess beneficial pharmacogalenical properties, such as good solubility in various solvents. Thus the solubility in ethanol is 12.7 mg/ml for Compound B in free form, as compared with 0.64 mg/ml for Compound A in free form.

The invention also provides a **process** for the preparation of a compound of formula Ib in free form or salt form, comprising

a) for the production of a compound of formula Ic

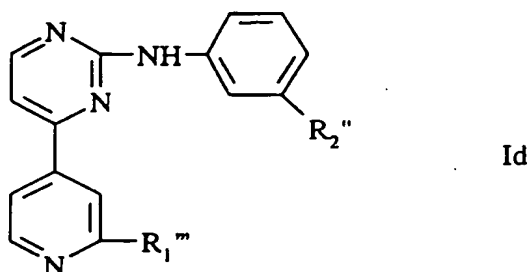


wherein R_1^{iv} is halogen of atomic number 17 or 35 and R_2'' is as defined above, reacting a compound of formula II



wherein R_2'' is as defined above,
with a reagent that introduces chlorine or bromine in the ortho position to the N-oxido group; or

b) for the production of a compound of formula Id



wherein R_1''' is phenyl or alkyl and R_2'' is as defined above,

reacting a compound of formula Ic with an organometallic compound of formula III



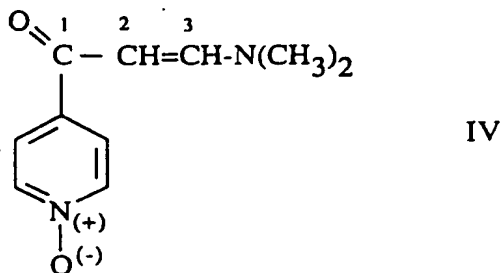
wherein Me is Al, Zn or Mg; n is 1 to 3; m is 0 or 1; X is halogen; and R_1''' is as defined above;

and recovering the resultant compound of formula Ib in free form or salt form.

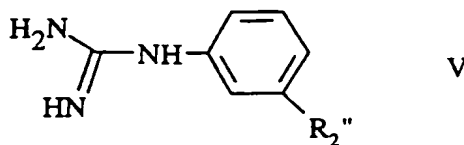
The process of the invention may be effected in conventional manner. Process variant a) can conveniently be performed by reacting a compound of formula II with phosphorous oxychloride or oxybromide, preferably in an inert solvent, e.g. acetonitrile, preferably at elevated temperature. R_1^{iv} preferably is chlorine. Process variant b) can be performed according to known organometallic reactions. It preferably is effected in the presence of a suitable catalyst, such as a Ni- or Pd-catalyst. Conveniently an aprotic solvent such as tetrahydrofuran is used. The reaction preferably is effected at room temperature or at elevated temperature.

The resultant compounds of formula Ib can be recovered from the reaction mixture and isolated and purified in known manner.

The starting material of formula II may e.g. be prepared by reacting the compound of formula IV



with a compound of formula V



wherein R_2 is as defined above.

Insofar as its preparation is not specifically described herein, a compound to be used as a starting material is either known, or may be prepared in known manner or analogously to known methods from known compounds.

The following Examples illustrate the invention. All temperatures are in degrees Celsius. m.p. = melting point.

Example 1: N-(3-chlorophenyl)-N-[4-(2-methylpyridin-4-yl)pyrimidin-2-yl]amine
[process variant b)]

Under argon, 952 mg of N-(3-chlorophenyl)-N-[4-(2-chloropyridin-4-yl)-pyrimidin-2-yl]amine (Compound A) and 18 mg of tetrakis-(triphenylphosphine) palladium are suspended in 10 ml of dry tetrahydrofuran. 2 ml of a 2M solution in heptane of trimethylaluminium are added and the reaction mixture is stirred at 67° for 2.5 hours. The dark solution is poured onto 60 ml of saturated sodium hydrogen carbonate and ice. The aqueous phase is extracted with ethyl acetate (3 x 20 ml) and the combined organic layers are extracted with 300 ml of 1N HCl containing 5 % methanol. The aqueous extract is neutralized with solid sodium hydrogencarbonate (pH 8) and the crystals are collected on a sinter funnel, washed 3 times with water, and dried at 60° under reduced pressure. The title compound is obtained (pale yellow crystals; m.p.: 157-159°).

Analogously as described in Example 1 the following compounds of formula Ib are obtained:

Example No.	R ₂ "	R ₁ "	m.p.
2 ¹⁾	CH ₃	CH ₃	137-140° ⁵⁾
3	Cl	C ₂ H ₅	166-168°
4	Cl	C ₆ H ₅	141°
5 ²⁾	OCH ₃	CH ₃	170°
6 ³⁾	CF ₃	CH ₃	156°
7 ⁴⁾	H	CH ₃	139°
¹⁾ starting from the compound of Example 15.2 in WO 95/9853 (Compound C) ²⁾ starting from the compound of Example 8 hereunder ³⁾ starting from the compound of Example 2 in WO 95/9851 (Compound D) ⁴⁾ starting from the compound of Example 9 hereunder ⁵⁾ m.p. of hydrochloride salt: 252°			

Example 8: N-[4-(2-chloropyridin-4-yl)pyrimidin-2-yl]-N-(3-methoxyphenyl)amine
[Process variant a)]

A solution of 2.94 g N-(3-methoxyphenyl)-N-[4-(1-oxidopyridin-4-yl)-pyrimidin-2-yl]amine [formula II; see A) hereunder], 3.31 g of tetraethylammonium chloride and 0.809 ml of pyridine in 18 ml of acetonitrile is heated to reflux and carefully (vigorous boiling at the beginning) treated with 2.80 ml of phosphorous oxychloride. The reaction mixture is heated at reflux for 2 hours, cooled to room temperature and poured onto 7 ml of a stirred solution of 28 % aqueous NH₃ and 60 ml of ice while the quenching temperature is maintained below 30°. After stirring overnight, the product is collected by filtration, rinsed with water containing 30 % acetonitrile and dried in a vacuum oven at 60°. The crude product is purified by passing a hot solution in toluene / methanol (9/1) over silicagel. The title compound is obtained (yellow crystals; m.p.: 154°).

Analogously as described in Example 8 the following compound of formula Ib is prepared:

Example No.	R ₂ "	R ₁ "	m.p.
9 ¹⁾	H	Cl	187°
¹⁾ starting from the corresponding compound of formula II; see B) hereunder			

The starting material of formula II may be prepared in the following manner:

A) N-(3-methoxyphenyl)-N-[4-(1-oxidopyridin-4-yl)pyrimidin-2-yl]amine

a) 4.93 g **m-anisidine** are dissolved in 8 ml of water and 11.8 ml of 37 % aqueous HCl and stirred at 70°. A solution of 3.77 g **cyanamide** in 3.8 ml of water is added dropwise (the temperature rises to 85°) and the reaction is allowed to proceed at 70-75° for 4 hours. After cooling to room temperature, the solution is poured onto a stirred solution of 5.3 g sodium carbonate in 24 ml of water. After stirring overnight the precipitate is isolated by filtration, rinsed with water and diethyl ether and dried in a vacuum oven at 40°. **Bis(3-methoxyphenyl)guanidine carbonate** is obtained (pale white crystals).

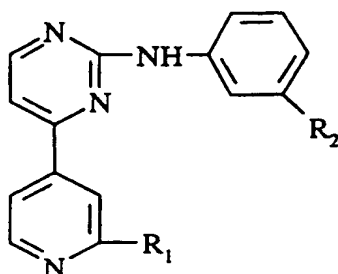
b) A mixture of 3.05 g bis(3-methoxyphenyl)guanidine carbonate and 3.00 g of **3-dimethylamino-1-(1-oxidopyridin-4-yl)-2-propen-1-one** in 30 ml of isopropanol is heated at reflux for 16 hours. After cooling to room temperature, the product is collected by filtration, rinsed with isopropanol and dried in a vacuum oven at 50°. The **title compound** is obtained (m.p.: 233°).

B) N-phenyl-N-[4-(1-oxidopyridin-4-yl)pyrimidin-2-yl]amine

The **title compound** (yellow crystals; m.p.: 250°) is prepared analogously as described under A) above, starting from **aniline** in place of **m-anisidine**.

Claims:

1. Use of a compound of formula I



I

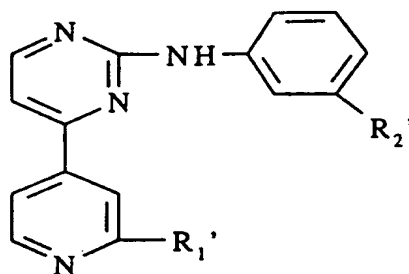
wherein

R₁ is halogen, phenyl or alkyl and

R₂ is hydrogen, halogen, alkyl, alkoxy or trifluoromethyl,

in free form or salt form, in the preparation of a medicament for the therapy of IgE-mediated diseases.

2. Use according to claim 1 of a compound of formula Ia



Ia

wherein

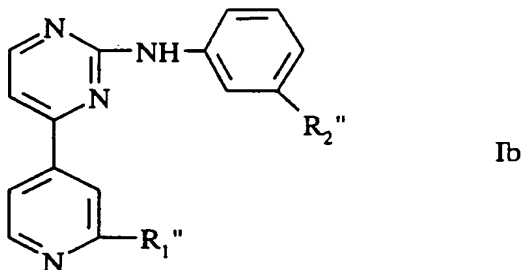
R₁' is halogen and

R₂' is halogen, lower alkyl or trifluoromethyl,

in free form or salt form.

3. Use according to claim 2 of a compound of formula Ia in free form or salt form wherein R₁' is halogen and R₂' is halogen or lower alkyl (a compound Iap).

4. Use according to claim 1, whereby the compound of formula I is
- a) N-(3-chlorophenyl)-N-[4-(2-chloropyridin-4-yl)pyrimidin-2-yl]amine (Compound A) or
- b) N-(3-methylphenyl)-N-[4-(2-methylpyridin-4-yl)pyrimidin-2-yl]amine (Compound B),
- in free form or salt form.
5. A method of treatment of IgE-mediated diseases which comprises administering a therapeutically effective amount of a compound of formula I as defined in claim 1 in free form or pharmaceutically acceptable salt form to a subject in need of such treatment.
6. A compound of formula I as defined in claim 1, which is of formula Ib



wherein

either R₁'' is halogen of atomic number 17 or 35 and

R₂'' is hydrogen or alkoxy,

or R₁'' is phenyl or alkyl and

R₂'' is hydrogen, halogen, alkyl, alkoxy or trifluoromethyl,

in free form or salt form.

7. A compound according to claim 6 in free form or salt form wherein R₂'' is other than hydrogen (a compound Ib_p).
8. The compound according to claim 6 which is N-(3-methylphenyl)-N-[4-(2-methylpyridin-4-yl)pyrimidin-2-yl]amine (Compound B) in free form or salt form.

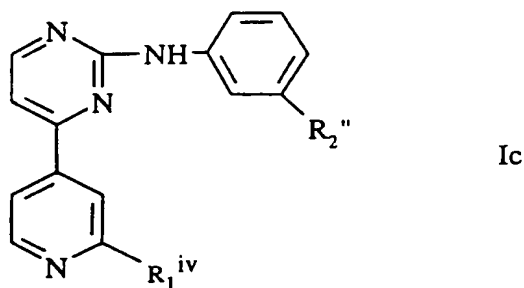
9. A **compound** according to claim 6 in free form or pharmaceutically acceptable salt form for use as a **pharmaceutical**,

or

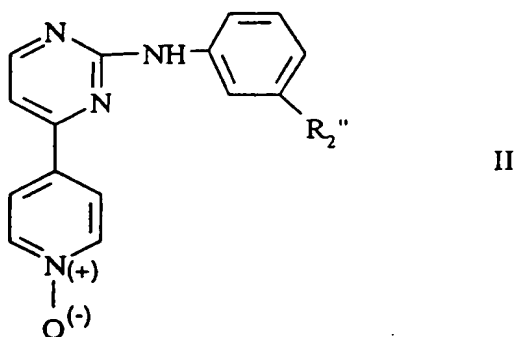
a **pharmaceutical composition** comprising a compound according to claim 6 in free form or pharmaceutically acceptable salt form together with at least one pharmaceutically acceptable carrier or diluent.

10. A **process** for the preparation of a compound according to claim 6 comprising

a) for the production of a compound of formula Ic

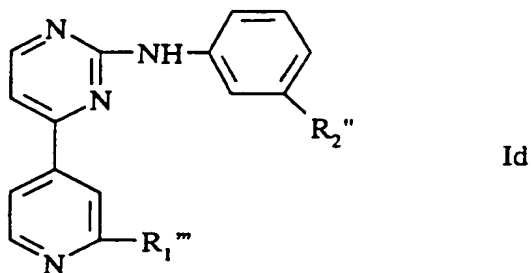


wherein R_1^{iv} is halogen of atomic number 17 or 35 and R_2'' is as defined in claim 6, reacting a compound of formula II



wherein R_2'' is as defined in claim 6, with a reagent that introduces chlorine or bromine in the ortho position to the N-oxido group; or

b) for the production of a compound of formula Id



wherein R_1''' is phenyl or alkyl and R_2'' is as defined in claim 6,

reacting a compound of formula Ic with an organometallic compound of formula III



wherein Me is Al, Zn or Mg; n is 1 to 3; m is 0 or 1; X is halogen; and R_1''' is as defined in this claim;

and recovering the resultant compound of formula Ib in free form or salt form.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/00060

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/04 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 09851 A (CIBA GEIGY AG ; ZIMMERMANN JUERG (CH)) 13 April 1995 cited in the application see claims; examples 1,2 -----	1,5,6
A	WO 95 09853 A (CIBA GEIGY AG ; ZIMMERMANN JUERG (CH)) 13 April 1995 cited in the application see claims; example 15.2 -----	1,5,6
A	EP 0 137 979 A (BOEHRINGER INGELHEIM LTD) 24 April 1985 see the whole document -----	1,5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

17 May 1999

Date of mailing of the international search report

26/05/1999

Name and mailing address of the ISA

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Authorized officer

Bosma, P.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/00060

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 5
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 5
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/00060

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